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HUMAN DRUGS

Current Good Manufacturing Practice in Manufacture, Processing, Packing or Holding of Large Volume Parenterals, and Request for Comments Regarding Small Volume Parenterals

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 212]

[Docket No. 76N–0099]

HUMAN DRUGS

Current Good Manufacturing Practice in the Manufacture, Processing, Packing, or Holding of Large Volume Parenterals

The Food and Drug Administration (FDA) is proposing to establish current good manufacturing practice (CGMP) regulations for large volume parenteral (LVP) drug products for human use. As defined in these proposed regulations, LVP's include drug products such as intravenous solutions, irrigating solutions, peritoneal dialysates, and blood-collecting units containing an anticoagulant solution. They are packaged in single-dose containers with a capacity of 100 milliliters or more and are terminally sterilized. Interested persons have until September 29, 1976, to submit comments.

In the FEDERAL REGISTER of February 13, 1976 (41 FR 6878) the Commissioner of Food and Drugs proposed substantial revisions in the CGMP regulations for finished human and veterinary drug products. In that proposal, the Commissioner also announced his intention to propose at future times further CGMP requirements for specific types of drug products, either by class or for individual products. One of the classes of drug products anticipated in that proposal as needing specific CGMP regulations is that of large volume parenteral drug products. LVP's constitute a relatively specialized class of drugs based upon their unique characteristics in both use and production. The primary use of many such products is not based upon traditional drug therapy, but rather upon a paramount need of a patient for basic body constituents when the patient is unable to consume, produce, or maintain medically necessary amounts. Because LVP drug products are usually administered to seriously weakened persons and generally large volumes of such products must be prescribed, a drug quality level of the highest magnitude is required. Furthermore, because the drugs in this class are administered parenterally, the risks arising from nonsterility are heightened. Thus, the smallest problem relating to the quality, strength, purity, or sterility of an LVP drug product can jeopardize the life of a patient. On the production side, LVP's are currently manufactured in the United States by a very few firms, each of which prepares enormous amounts of drugs in this class. As discussed later in this preamble, recent problems within the LVP industry have suggested a need for priority action and, at the same time, they provide an opportunity for quickly raising all suppliers to the level of current good manufacturing practice. Therefore, FDA has developed specific criteria for the manufacture, processing, packing, or holding of LVP drug products to assure the highest possible standards for the finished product.

These criteria are already generally well known to the affected industry through various contacts between FDA and the industry during the development of this proposal. Some of these contacts resulted from several extensive recalls of marketed LVP drug products that failed to meet standards of quality or purity. Such recalls have involved individual lots of drug products and, in some instances, the entire LVP drug product production where significant manufacturing deficiencies in the plant were found by FDA during a plant inspection. As a result, the affected firms made changes in their manufacturing procedures and plant design after consulting with FDA. During such consultations, the criteria proposed herein were made known to the firms.

In addition, the Commissioner released an earlier draft of this proposal to the public on February 14, 1975 (40 FR 6811).

While these proposed provisions are not yet requirements, the Commissioner believes that current practices of LVP drug product manufacturers already comply with most of these provisions. Where there are differences, the Commissioner believes that manufacturers are developing the data necessary to effect changes to comply with the proposed requirements.

Because of the critical nature of both the production and use of LVP drug products and evidence that not all manufacturers could assure the level of microbiological quality required for LVP drug products, FDA, in late 1971, began an intensive review and evaluation of LVP production. This review was first limited to specific, individual manufacturing or container-closure problems. In 1973, the review expanded to a broad survey of the industry that included extensive sampling of LVP drug products, comprehensive drug establishment inspections by specially trained investigator-engineer-microbiologist teams, and detailed discussions between the industry and FDA. These discussions with LVP drug product manufacturers have provided the industry an opportunity to comment, both orally and in writing, on the technical aspects of LVP drug product production that FDA considered pertinent to good manufacturing practice. In addition, since certain LVP drug products are new drugs, the Commissioner has been able to consider information submitted under the provisions of section 505 of the Federal Food, Drug, and Cosmetic Act. Specifically, FDA has reviewed information in new drug applications (21 CFR Part 314)) regarding the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of LVP drug products. The information developed by FDA during this 4-year period, including industry discussions, is the basis for this proposal.

Copies of documents relating to the discussions with industry are on file with the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852. Such documentation includes the initial points for discussion and summary minutes of the meetings.

This proposal includes for the first time in CGMP drug regulations specific well-defined process standards. The Commissioner has already established comparable precise standards for certain biological products (21 CFR Subchapter F) and for low-acid foods in hermetically sealed containers (21 CFR Part 128b). It is important to realize that explicit detail is necessary to provide assurance that the methods and facilities used and the conditions of production are adequate in design and application to preclude microbiological and pyrogenic contamination of LVP drug products. The industry and FDA both recognize that sampling and testing of finished products alone cannot provide the necessary assurance of drug product quality. Without standardized procedures of demonstrated reliability of production and sterilization processes, assurance of quality could only be obtained through full testing of every unit. Testing to this extent is, of course, not practicable.

The Commissioner intends for CGMP regulations to become binding specific requirements that must be complied with; failure to do so shall render an LVP drug product adulterated under section 501 (a) (2) (B) of the act. Section 701(a) of the act empowers the Commissioner to promulgate substantive rules to facilitate enforcement of the act's other provisions. *National Nutritional Foods Ass'n* v. *Weinberger*, 512 F. 2d 688 (2d Cir. 1975); *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); *CIBA Corp.* v. *Weinberger*, 412 U.S. 640 (1973); *Weinberger* v. *Bentex Pharm. Inc.*, 412 U.S. 645 (1973). Publication of proposed regulations establishing current good manufacturing practice in the manufacture, processing, packing or holding of large volume parenterals for human use will allow all members of the industry an opportunity to participate in their preparation and to note the level of performance expected of them. Binding regulations will also serve to inform courts of expert judgments of FDA regarding current good manufacturing practice for LVP drugs in the United States; this will expedite and assist enforcement proceedings to assure compliance with section 501(a) (2) (B) of the act. The legal status of the CGMP regulations is set forth in § 210.1, proposed in the FEDERAL REGISTER of February 13, 1976 (41 FR 6878).

RELATION TO CURRENT GOOD MANUFACTURING PRACTICE REGULATIONS IN PARTS 210 AND 211

Section 212.1 provides a specific statement regarding the applicability and relationship of the more general CGMP regulations in Parts 210 and 211 to manufacturers of LVP drug products. Unless otherwise explicitly provided, the regulations in 21 CFR Part 210—Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs: General; and 21 CFR Part 211—Current Good Manufacturing Practice for Drug Products are applicable to all drug products, including LVP drug products. Therefore, it must be clearly understood that the regulations proposed

at this time will be in addition to, and supplement, the more general CGMP regulations of Parts 210 and 211 as proposed in the FEDERAL REGISTER of February 13, 1976. To determine the requirements for complying with current good manufacturing practice for LVP drug products, both the general CGMP regulations and the specific CGMP regulations for LVP drug products must be applied. Provisions in the general CGMP regulations are not repeated in the specific CGMP regulations for LVP drug products. However, a provision in Part 212 that supplements a corresponding requirement in Part 210 or 211 is keyed numerically to the regulations in Part 210 or 211. To trace a corresponding section, refer to the last portion of the section number. For example, definitions are in §§ 210.3, 211.3, and 212.3; requirements regarding responsibilities of the quality control unit are in §§ 211.22 and 212.22.

RELATION TO MANUFACTURING PRACTICES SUBJECT TO APPROVED NEW DRUG APPLICATIONS

A significant number of LVP's are subject to new drug applications (NDA's) that were approved under earlier and possibly less specific or less rigorous standards. The LVP current good manufacturing practice regulations are issued under section 501(a)(2)(B) of the act and are applicable to all LVP drug products, regardless of their "new drug" status. Failure to comply with the CGMP specifications renders the product adulterated and subject to regulatory action. New drug applications are covered by section 505 of the act. The "manufacturing controls" portion of an NDA contains the commitments of a manufacturer regarding the methods he will use in the manufacture, processing, packing, and holding of the product. Failure to abide by these commitments takes the product outside the marketing privilege conferred by the NDA and renders the product subject to regulatory action as a "new drug" not covered by an approved NDA. It is the position of FDA that an LVP drug product must be manufactured in accordance with the higher standard or more rigorous specification applicable to the product under the CGMP regulations and the NDA commitments. If, for example, the sterilization process standard proposed in these CGMP regulations is adopted and exceeds the sterilization process commitment undertaken in an approved NDA, the product will be deemed adulterated unless the CGMP standard is met, notwithstanding compliance with the NDA commitment. At the same time, if the same NDA sets forth requirements for the LVP product container and closure system that are more rigorous than those in the CGMP regulations for LVP's, the product will be deemed to be outside the NDA and subject to regulatory action if the NDA standards are not met, notwithstanding compliance with CGMP regulations.

This result is intended by the act, which subjects all drugs to the "current good" standards of manufacturing, even though they were approved for marketing on the basis of earlier, lesser standards. Indeed, FDA has long permitted persons holding an approved NDA for a drug to implement changes in the methods, facilities, and controls used in manufacturing without prior approval if the changes give increased assurance that the drug will have the characteristics of identity, strength, quality, and purity that it purports to possess (21 CFR 314.8(d)(3)). NDA specifications higher than CGMP standards, on the other hand, are adopted by the manufacturer presumably because he and FDA believe them necessary or desirable to assure the quality of his product; changes in these specifications that will not provide increased assurances of product quality may not be implemented without prior authorization of FDA (21 CFR 314.8(c)).

These proposed regulations specify some of the facilities, types of equipment, processes, and controls that must be used to obtain a desired result for the LVP drug product. It is not the intent of FDA, however, to curtail technological advance in the form of new facilities, types of equipment, processes, or controls where such advance accomplishes at least the results attainable by strict compliance with these regulations. Nor is it the intent to require compliance when to do so would lead to the alteration, degradation, or instability of the end product. The Commissioner realizes that in rare cases it may not be possible for an LVP drug product to be made in compliance with the proposed CGMP regulations, particularly the sterilization process in § 212.240, because of unique characteristics in the drug product that would be impaired, altered, or destroyed if full compliance were attained. The Commissioner has not attempted, however, to determine which specific drug products, if any, cannot be processed in compliance with the proposed regulations. It is the responsibility of every manufacturer of an LVP drug product to determine whether compliance is feasible, and, if not, to have data to support any exceptions from the proposed minimal sterilization process. For those drug products that must be processed under lesser standards than those proposed in these CGMP regulations and that are the subject of a new drug application approved on the basis of those lesser standards, a supplement to the NDA is required establishing the need for lesser standards. If the supplement is approved, the drug product is exempted from the CGMP regulations for that process or other requirement. For LVP drug products manufactured under different standards that are equal to or exceed these proposed CGMP regulations and are subjects of existing approved NDA's, the NDA requirements continue as a commitment. For drug products not able to meet the minimal sterilization process and not subject to section 505 of the act, the Commissioner advises that at this time the data to support any such exceptions shall be maintained by the manufacturer and will be reviewed and evaluated during factory inspections conducted under section 704 of the act. The proposed § 212.5 sets forth the foregoing policy.

In order to determine whether exceptions to this policy are anticipated, the Commissioner requests specific information regarding those LVP drug products that cannot withstand the proposed sterilization process. Therefore, each manufacturer should, during the time period provided for comments on these proposed regulations, identify any of his LVP drug products, whether or not now covered by an approved NDA, that cannot be manufactured in compliance with the proposed minimal sterilization process. The Commissioner will evaluate the need for particular deviations during the preparation of the final regulations on this proposal.

GENERAL PROVISIONS (SUBPART A)

1. In proposed § 212.3(b)(1) the term "large volume parenteral" is defined as a terminally sterilized aqueous drug product packaged in a single-dose container with a capacity of 100 milliliters or more and intended to be administered or used in humans. This includes intravenous infusions, irrigating solutions, peritoneal dialysates and blood collecting units with anticoagulant. While large volume parenteral drug products are considered by some to be only for intravenous use, there is no universally accepted definition that limits such drug products to intravenous use. For the purposes of this part, the meaning of LVP drug product is broadened to include several kinds of sterile fluids that are used under circumstances where failure to meet standards of microbiological quality place the patient at risk.

These proposed regulations apply only to LVP drugs for human use. This differs from the general CGMP regulations in Parts 210 and 211, which apply to both human and veterinary drugs. Almost all contacts and discussions with the industry during development of this proposal involved drugs for human use. Thus, the proposed regulations are based on information specific to LVP drug products for humans. In addition, the Commissioner notes that a significant portion of LVP drug products intended solely for veterinary use are sterilized by means other than those covered in this proposal, and that certain other requirements for such veterinary products differ significantly from those for human-use products, e.g., veterinary LVP drugs need not be pyrogen-free. For these reasons, CGMP regulations for veterinary LVP drug products are not included in this proposal and will be considered at a later time.

Biological drug products are not included in the term "large volume parenteral" because they are not terminally sterilized, and many of the proposed requirements would not be appropriate for the manufacture of such products. Biological drug products are regulated under section 351 of the Public Health Service Act (42 U.S.C. 262) and are subject to the general CGMP regulations in Parts 210 and 211 as well as the stand-

ards set forth in Parts 600 through 680 (21 CFR Parts 600 through 680).

2. Proposed § 212.3(b)(2) defines the term "controlled environment area." The weighing, mixing, filling, transfer, and gowning areas must be environmentally controlled in accordance with the standards of air quality and the requirements for lighting and construction that are specified in this part to minimize contamination from air-borne particulates, including microorganisms.

3. In proposed § 212.3(b)(3), (5), (6), and (12) the terms "F_o," "heat distribution study," "heat penetration study," and "sterilization process," are defined for use in testing procedures to determine the adequacy of the sterilization process.

4. In proposed § 212.3(b)(4) and (7) the terms "HEPA filter" and "laminar flow" are defined. Elsewhere in the regulations, in §§ 212.77 and 212.222 are requirements for high efficiency particulate air (HEPA)-filtered, laminar-flow air equipment to be used at the filling line and microbiological testing area. Air of this high quality in these critical areas of drug product exposure is already widely used throughout the industry.

Organization and Personnel (Subpart B)

1. Proposed § 212.22 establishes specific responsibilities for the quality control unit. The proposed regulations require that before a plant, process, procedure, or container-closure system is used in LVP drug product production, it must be tested and accepted or rejected by the quality control unit. The quality control unit has the responsibility and authority to accept or reject the design, engineering, and physical facilities of the plant, the equipment, the manufacturing processes and procedures, and the container-closure system. In addition, modifications in production systems must first be approved by the quality control unit before implementation.

2. Proposed § 212.29 establishes requirements to be followed by personnel when entering or leaving a controlled environment area. Appropriate nonlinting garments are required to be worn while in the controlled environment area and are prohibited from being worn outside of the controlled environment area, including the changing area. The basic provisions of this proposed section are already extensively practiced by the LVP drug product industry.

Buildings and Facilities (Subpart C)

1. Proposed § 212.42 sets forth general design and construction features for LVP drug manufacturing facilities as well as specific construction features for controlled environment areas within these facilities. To preclude the physical features from becoming a source of contamination by particulates, the Commissioner believes the walls, floors, ceilings, fixtures, and partitions in controlled environment areas must have surfaces that resist flaking and other deterioration and are suitable for cleaning. To preclude possible contamination, this section prohibits fixed pipes or conduits over exposed components, in-process materials, drug products, and drug product contact surfaces, including drug product containers and closures after final rinse. All pipes or conduits for air or liquid in each physically separated area are required to be identified by name, color code, or other suitable means as to their content. Manufacturers have long recognized the importance of using materials that are easily cleaned and that will not flake or deteriorate. For the most part, plant, equipment, and facilities already have been designed and constructed to meet the proposed requirements. Therefore, the Commissioner believes that the majority of firms already conform to this proposed section.

2. Proposed § 212.44 requires lighting fixtures in controlled environment areas to be constructed and installed in a manner to prevent any accumulation of dust and to facilitate cleaning. Such fixtures must also be enclosed to prevent scattering of any material in case of breakage. The Commissioner believes that building construction in most plants currently incorporates the features proposed here.

3. Proposed § 212.45 establishes specific requirements for locating and equipping gowning areas. This requirement is designed to assure that robing accommodations will minimize the likelihood of particulate contamination of the special garments to be worn in controlled environment areas.

4. Proposed § 212.47 requires that the facilities used for LVP production include a compressed-air processing and distribution system. The air produced by such a system shall meet certain requirements, which are set forth in § 212.223 and discussed at length in this preamble under Subpart L.

5. In proposed § 212.49 specific requirements are added for systems handling water and other liquids to ensure the quality of the material handled. Pipelines for the transmission of water for injection and other liquid components are required to be of welded stainless steel equipped for sterilization with steam, except that sanitary stainless steel lines with fittings capable of disassembly may be immediately adjacent to the equipment or valves that must be removed from the lines for servicing. Pipelines capable of disassembly for manual cleaning may be used for liquid in-process materials.

This section would also prohibit filters at any point in the piping system carrying water for manufacturing or final rinse to prevent microbial or pyrogen contamination attributed to improperly maintained in-line filters.

In the Federal Register of March 14, 1975 (40 FR 11865), the Commission published final regulations regarding fibers, particularly asbestos-form particles, in drugs for parenteral injection. These requirements are now in the CGMP regulations in §§ 211.40(j) and 211.55 (21 CFR 211.40(j) and 211.55) (and in §§ 211.72 and 211.94(c) in the proposed revisions of the CGMP regulations published in the Federal Register of February 13, 1976). In part, the existing CGMP regulations require that containers for parenteral drugs be cleansed with water that has been filtered through a nonfiber-releasing filter of maximum pore size of 0.22 micron (or 0.45 micron if the manufacturing conditions so dictate).

The requirements for parenteral drug products regarding filtration to remove fibers apply to all parenteral drug products including LVP drug products. Because of the high quality standards for final rinse water that are being proposed for LVP drug products, the Commissioner is seeking sufficient information to determine whether filtration of the final rinse water should continue to be required. Therefore, he finds it appropriate to request information and comments regarding the need to filter the final rinse water to remove fibers and the placement of filters if such filtration is desirable.

6. In proposed § 212.49(c) the length of unused piping in systems handling water for manufacturing and final rinse and other liquid components is restricted to prevent the accumulation of stagnant fluid and possible subsequent bacterial buildup that could contaminate the fluid system. The proposed limits on the pipe length will allow sufficient turbulence and interchange of fluid when there is flow in the principal line. This phenomenon of turbulence and fluid interchange is an engineering principle that is well recognized. The proposal for LVP pipelines is based on similar kinds of requirements; for example, sanitary standards for bulk transport of milk set forth in "3-A Sanitary Standards For Stainless Steel Automotive Milk and Milk Products Transportation Tanks For Bulk Delivery and/or Farm Pick-Up Service," *Journal of Milk and Food Technology*, Vol. 34 No. 11, November 1971 (on file in the office of the Hearing Clerk, Food and Drug Administration).

7. Proposed § 212.51 draws attention to potential problems of microbiological contamination resulting from improperly designed drainage systems. Plumbing must be designed to prevent backflow of production or sanitary wastes from occurring.

Equipment (Subpart D)

1. Proposed § 212.63 requires that equipment such as guide rails, diverters, and transfer mechanisms that contact glass bottles shall be designed to prevent damage to the bottles. Rough handling of bottles can result in small cracks or chips that might allow the drug product to become contaminated. This problem is already well recognized by manufacturers, and equipment today is generally designed to protect against this kind of damage.

2. Proposed § 212.65 requires that equipment be constructed so that its surfaces shall not affect the safety, identity, strength, quality, or purity of the LVP drug product.

3. Proposed § 212.67 discusses the requirements for equipment cleaning and maintenance that must be followed and included in a written procedure and

cleaning schedule. One of the requirements is the provision that all equipment and surfaces that contact components, in-process materials, drug products, or drug product contact surfaces be rinsed with water meeting the quality standards for water used as a component of the LVP drug product immediately prior to such contact.

4. Proposed § 212.68 discusses the equipment used in the manufacture, processing, packing, and holding of large volume parenterals that is sophisticated and must function with great precision. This equipment must be periodically checked, calibrated, examined, or tested for proper functioning and accuracy. Therefore, the Commissioner proposes that all such equipment be examined according to written schedules and procedures and that the results of such work be recorded.

5. In proposed § 212.72, there is a requirement that the integrity of air and solution filters be established before they are used. In addition, the integrity of filters used for filtering LVP drug products are required to be verified before and after the filtering operation. If a solution filter used for any lot of an LVP drug product fails the test, all materials filtered through it shall be rejected. However, the Commissioner believes that refiltration can be permitted as long as the entire process does not exceed the 8-hour process time specified in § 212.111 and so proposes. Solution filters are required to be sterile at the time of installation.

6. Proposed §§ 212.73, 212.74, and 212.75 set forth specific requirements for the equipment used in sterilization of LVP drug products. Large volume parenteral products can only have the quality characteristics that are commensurate with the quality of the components and equipment used. The sterilization procedure is a critical step in the production of sterile and pyrogen-free LVP drug products. The quality of these products can be assured only by employing sterilization equipment and procedures that are capable of accurately reproducing the microbial lethality desired.

These proposed sections establish requirements for sterilization equipment that recognize the three most widely used methods of heat sterilization: steam or air-steam mixtures (§ 212.73), superheated water (§ 212.74), and steam with hydrostatic pressure (§ 212.75). The equipment requirements for each method are described in detail to assure uniformity of temperatures and pressure during sterilization.

Although this subpart discusses the requirements for three different heat sterilization procedures, alternative procedures may be used as provided for in § 212.5. Irrespective of the sterilization procedure, it may not be used for LVP drug products until it has been tested and approved by the quality control unit.

7. Proposed § 212.76 establishes criteria for heat exchangers. The pressure differential of heat exchangers must be monitored and monitoring records must be maintained. Again, the purpose of this requirement is to contribute to the assurance of microbial quality.

8. Proposed § 212.77 requires that HEPA-filtered, laminar-flow air be used over the filling line and in the area where microbiological testing is performed because air may be a significant source of contamination. Air in both areas must be of the highest quality. In the filling area, the containers are open and thus vulnerable to contamination. To rely on the test results with a high degree of confidence, it is also essential that the microbiological testing have high quality air. This section also requires that the laminar-flow equipment be monitored according to a written program and records be maintained of the test and any resultant corrective actions. Generally, the LVP drug product industry already meets these standards.

9. Proposed § 212.78 requires that air vents of all stills and tanks that hold water for manufacturing or final rinsing, water for cooling the drug product after sterilization, liquid components, and in-process solutions be equipped with nonfiber-releasing sterilizable filters capable of preventnig microbial contamination of the contents. Such filters shall be sterilized and installed aseptically.

10. Proposed § 212.79 requires that pumps moving water for manufacturing or final rinsing, water for cooling the drug after sterilization, and in-process or drug product solutions be designed to utilize water for injection as a lubricant for the seals.

Control of Components, Drug Product Containers, Closures, and In-Process Materials (Subpart E)

1. Proposed § 212.84 prescribes requirements applicable to the testing and approval or rejection of components, containers, and closures. All components must periodically be subjected to microbiological examinations and be free of heat-resistant spores or other microbiological contaminants that may affect the quality of an LVP drug product.

In addition, because of the nature of LVP drug products, the Commissioner concludes that special protection must be provided to assure a pyrogen-free product. Therefore, in addition to requiring the pyrogen test on the final drug product, the Commissioner is proposing to require that each shipment of each lot of components, drug product containers, and closures be tested for pyrogenic properties prior to release by the quality control unit. Lots of materials that produce a pyrogenic reaction shall be rejected, but may be reprocessed. This is in accord with current good manufacturing practice in the LVP industry.

2. Proposed § 212.94 supplements § 212.84 with respect to chemical and physical characteristics of the container-closure system. Because of the critical nature of the container-closure system, which must protect the sterility of the drug after that state has been achieved, it is essential that containers and closures be of optimal quality. Since containers and closures employed in the manufacture of LVP drug products are unique to this industry, the Commissioner concludes that special procedures utilized in some LVP manufacturing today should be required for the control of all LVP drug product quality. This proposed section sets forth such requirements.

Before any container-closure system may be used for LVP drug products, it must first be tested and approved by the quality control unit. As with other systems that have been so evaluated and accepted, changes may not be made until the proposed changes are reviewed and approved by the quality control unit.

In view of the importance of the container-closure system, the Commissioner proposes to require that each shipment of each lot of containers and closures be sampled and tested for physical characteristics according to a statistically valid sampling plan. Thus, even if containers from the same manufactured lot are received at two different times, this section requires each shipment to be sampled and tested for physical characteristics. If the supplier of the containers or closures is changed, 100 percent inspection for physical defects shall be performed until the reliability of the new supplier has been established.

Production and Process Controls (Subpart F)

Many of the requirements proposed in this subpart are matters that are specific to parenteral production but have their conceptual roots in the general requirements for finished pharmaceuticals in Part 211. For example, the requirement that procedures be written and documented is found throughout Part 211; however, the requirement for a procedure for flushing static lines is specific to parenterals and therefore appears in this proposal.

The more significant proposed requirements that are specific for LVP drug products are as follows:

1. Proposed § 212.100(a) requires that the processes and procedures used in the production of the drug product be tested and determined adequate by the quality control unit.

2. In proposed § 212.100(b) written procedures are required for flushing all static lines to prevent any growths of microorganisms from being added to the production system. In addition, procedures must be established to specify the action to be taken with regard to the material in the sterilizer when the automatic system fails or the alarm signals a malfunction.

3. In proposed § 212.104 requirements regarding calculation of yield have been expanded over the more general CGMP regulations to take into account procedures peculiar to LVP drug production such as drug product loss due to line flushing.

4. Proposed § 212.111 establishes maximum production time limits. To prevent excessive growth of microorganisms prior to sterilization, and to protect against generation of pyrogens, the Commissioner proposes that specific time limitations be placed on certain production

phases. Although the industry survey revealed no specific industry practice in this area, all firms felt that time had to be limited. It is, therefore, proposed that an 8-hour limit be established as the maximum permissible time between addition of water for manufacturing (frequently termed "product make-up water") to the mix tank and the exposure of the last container to the sterilization process.

5. In proposed § 212.116 there is a requirement that prior to filling, LVP drug products must be filtered through a filter system having a final mean porosity of 0.45 micron. However, the Commissioner recognizes that this limitation may not be practicable for viscous drug products and proposes to permit a larger porosity filter to be used to achieve a flow rate consistent with the maximum production time limitation. The length of time a filtration system can be used without cleaning or filter replacement is limited to 8 hours.

6. Proposed § 212.117 requires that after the sterilization process and before release for marketing, all LVP drug products be visually examined for particulate matter. Alternate methods of examination may be used provided such methods are as effective as a visual examination. Any drug product found to contain particulate matter must be rejected.

7. Proposed § 212.118 permits reuse of sterilized glass containers during production operations. Such containers usually come from lots that have been sterilized but do not meet some specification that does not affect the integrity of the container itself.

This section proposes careful evaluation of such containers, including data concerning the effects of repeated sterilization on the container.

PACKAGING AND LABELING CONTROL (SUBPART G)

Proposed § 212.130 is intended to recognize the importance of suitable packaging for shipping sterile, large volume drug products covered by these regulations.

HOLDING AND DISTRIBUTION (SUBPART H)

1. Proposed § 212.142 requires that written procedures describing the storage of LVP drug products include specific directions regarding the stacking of cases. Limitations of stacking height, for example, will eliminate undue stress on the container-closure system.

2. Proposed § 212.150 requires manufacturers to establish and follow proper shipping procedures and to discontinue the services of transportation companies that are found to routinely mishandle LVP drug products in a way that could jeopardize the integrity of the products. While this may be a relatively new concept to some manufacturers, the Commissioner is aware that a number of drug manufacturers routinely monitor the conditions under which their products are shipped.

LABORATORY CONTROLS (SUBPART I)

In proposed § 212.167, laboratory controls, which supplement the broader requirements in the general CGMP regulations, relate specifically to testing for pyrogens, particulate matter, and sterility.

First, pyrogen testing is proposed to be performed at certain specific times in the manufacture of LVP drug products. This would be at the times of the filling of the first and last containers in a batch and when containers are filled after resumption of operations following any significant stoppage of production. The Commissioner believes that samples drawn at these points will reflect "worst" conditions, and if these are found satisfactory, the material produced in the interim can be expected to be of suitable quality. The pyrogen test method proposed is the United States Pharmacopeia (U.S.P.) method; however, any method that is equivalent to the U.S.P. method may be used. The pooling of material for testing is not permitted except where there is insufficient material to test. Such cases should be the extreme exception.

The U.S.P. in the first supplement to its 19th revision has included a method for determining the degree of contamination with, and limit for, particulate matter for large volume single-dose intravenous infusions, one type of LVP drug product. The method and standards in the U.S.P. for particulate matter are proposed; however, alternative methodology may be used if equivalent to the U.S.P. method.

The third test proposed is for sterility of the lot. Again, the U.S.P. testing procedures (membrane filtration) or equivalent is proposed.

RECORDS AND REPORTS (SUBPART J)

Generally, this proposed subpart summarizes the records and reports required to be maintained and, for convenience, cites cross-references to pertinent sections elsewhere in the proposed regulations.

AIR AND WATER QUALITY (SUBPART L)

1. Proposed § 212.220 establishes general requirements for air and water quality. In considering the need for requirements relating to the manufacturing and processing of LVP's, the Commissioner recognizes the importance of high quality air and water.

No article is used more extensively in the manufacture of LVP drug products than is water. Since the problems associated with LVP's in the past have been microbiologically oriented, it is mandatory that microbiological quality limits be established for water, which, when exceeded, require the initiation of corrective action.

Before the intensified efforts of the last several years, industry had not considered the air in LVP plants as a source of microbial contamination except in the area directly over the filling line. Since microbial control is essential throughout the plant, it is only prudent that attention be given to environmental air in production areas and that quality limits be proposed for air in critical areas.

This section therefore proposes general requirements for air and water quality and requires written procedures to specify appropriate corrective action when established specifications are not met.

2. Proposed §§ 212.221, 212.222, and 212.223 identify air quality requirements for a number of specific plant areas where there is a potential for LVP drug product contamination. The Commissioner notes that other Federal Government organizations have had considerable experience with "contamination control" in areas not related to drug manufacture. Examples are found in the Contamination Control of Aerospace Facilities, U.S. Air Force Technical Order (T.O.) 00-25-203, Warner Robins ALC/MMSTD, Warner Robins AFB, GA-31098 and Clean Room and Work Station Requirements, Controlled Environment (Fed. Std. No. 209B), General Services Administration Specifications Activity, Printed Materials Supply Division, Bldg. 197, Naval Weapons Plant, Washington, DC 20407 (on file in the office of the Hearing Clerk, Food and Drug Administration). In considering these Federal requirements for nondrug facilities and the current practices of the LVP drug industry, the Commissioner concludes that many of these requirements for nondrug facilities are clearly applicable to drug production facilities. Therefore, as a starting point for this proposal, the air quality for critical areas of possible drug product exposure is defined in these proposed sections. The principle is that air coming into contact with a vulnerable product or process must be of a quality that will not unduly jeopardize the product by contributing significant undetected contamination. Monitoring of air quality on a regular, routine basis is essential to maintaining appropriate air quality. Air over filling lines has generally been HEPA filtered; however, it has not been monitored by industry to demonstrate that it meets the requirements of a class standard. It is therefore proposed that such air be HEPA filtered and that it be monitored for particulates during production so that standards can be set, deviation from the norm can be detected, and remedial action taken when necessary. The Commissioner believes that the proposed air quality requirements are broad enough to provide reasonable latitude for all firms to comply and yet be a meaningful quality assurance standard. As additional experience is gained with regard to the relationship of air quality to drug quality, the Commissioner will consider revisions in these proposed CGMP regulations.

Attention must also be given to compressed air. It is proposed that compressed air be filtered to meet the air quality requirements at the point of use.

The industry has suggested that filtration will produce air of the particulate quality desired and will not necessitate the expensive replacement of compressors and distribution lines. Compressed air is presently being dehumidified by the industry to prevent condensation and thus possible microbial contamination in the distribution lines. The Commissioner also proposes that compressed air be supplied by an oil-free compressor and be free of oil and oil vapor unless such compressed air is vented to a noncontrolled-environment area. The Commissioner believes that compressed air must be supplied free of oil and oil vapor because he is not aware of filters that can remove oil vapor. However, the Commissioner recognizes that some compressed-air-operated equipment cannot be operated without a lubricant. Therefore, the proposed regulations would allow for the use of compressed air containing oil and oil vapor when such air is vented directly to a noncontrolled environment area.

3. Proposed § 212.224 establishes quality standards for water that is used for cleansing or initially rinsing drug product containers and closures, and drug product contact surfaces or equipment. Such wash and rinse water need not have the same requirements as final rinse water because of the further rinsing effect imparted by the subsequent use of the higher quality final rinse water. The proposed microbial limit for water for cleansing and initial rinsing is 50 microorganisms per 100 milliliters in three consecutive samples.

The 1973 industry survey revealed that setting specifications and monitoring this water for conformity to specifications was not a general industry practice. Testing such water at that time showed that some plants had significant contamination. Although monitoring and controlling this water is today an industry practice, the microbial limit established may vary among individual firms. As with other specifications in these proposed regulations, the Commissioner invites comments on reasonable limits for microbial content of this water that will demonstrate control of the system producing the water and that will result in assurance of quality of the LVP drug product.

4. Proposed § 212.225 contains specific standards for water used as a component of an LVP drug product or as a final rinse for equipment or drug product contact surfaces. Water for injection, as defined in the U.S.P., is the ingredient of greatest volume used to prepare LVP drug products and is the basis for the proposed requirements for water used as a component of such parenterals. Because the Commissioner recognizes the need to build quality into the product by means of knowing the quality of component parts associated with its manufacture, he is also proposing certain microbiological quality levels as specifications for water used for certain critical purposes. Microbial limits, proposed in this section and in §§ 212.224 and 212.226, are new to CGMP regulations. However, some manufacturers already meet these limits, and virtually all manufacturers have established microbial limits for water used in the manufacture and cooling of LVP drug products and the cleaning and rinsing of drug product contact surfaces. Therefore, the Commissioner has concluded that a reasonable, finite level of microbiological population in water should be established to determine when water quality is unacceptable and the production process can no longer assure a safe and sterile end product. The Commissioner welcomes comments on these proposed microbial limits and invites the submission of alternative specific limits, together with information supporting them or challenging the limits proposed in this notice.

The microbiological quality limit proposed for water for manufacturing or final rinsing is not more than 10 microorganisms per 100 milliliters in three consecutive samples of 250 milliliters or more taken from the same site. This microbial level was selected because data from LVP manufacturers reviewed during the 1973 survey indicated that this limit is reasonable and can be consistently met. Allowance for three consecutive samples from the same site to exceed the limit before action must be taken will permit sampling and testing errors to be identified as such. Thus, the results of one test will not condemn the system. When produced with such a quality, it is expected that such water will be stored and handled in a manner that will maintain that level of quality. Thus, it is proposed that the water be stored in a system at temperatures of at least 80° C under continuous circulation, or, if stored at ambient temperatures or lower, that the water be dumped to drain at least every 24 hours. The Commissioner believes that almost all manufacturers have adopted similar requirements for adequate handling and storage of this high quality water.

5. Proposed § 212.226 contains microbial standards for water for drug product cooling. This section proposes that water used for cooling the product after sterilization be treated by an appropriate method (i.e., chlorination or sterilization) to reduce the microbial population to one viable organism per 100 milliliters in three consecutive samples of 1 liter or more from the same site. The Commissioner finds that drug product cooling water must be of extremely high quality to eliminate the possibility of introducing microorganisms from contaminated cooling water into the LVP drug product after the sterilization process is complete. While the 1973 survey revealed that it was not universal industry practice to test such cooling water for microbial contamination, recent information indicates that most manufacturers recognize the importance of using a high quality cooling water and have established microbial standards for such water.

6. Proposed § 212.227 prohibits the use of volatile additives in boilers that supply steam that contacts drug product contact surfaces. Because steam is used extensively throughout the production of LVP drug products, it is necessary to be assured that such steam does not contaminate the drug product.

7. Proposed §§ 212.231, 212.232, and 212.233 require monitoring of air and water quality. To control the microbial flora of the environment, there must be some knowledge of what is present. The 1973 survey showed that industry had very little information in this area. Since that time, firms have established programs and have generated data to identify the normal microbial experience in each plant. Section 212.231 requires that the microbial flora of the plant be monitored according to a sampling and testing program designed to determine whether the plant and equipment, manufacturing processes, and control procedures continue to be effective for LVP drug production. One of the main purposes of such a program is to obtain data as to the probable contribution to the total load of contamination made by each integral part of the process. Specifically in §§ 212.232 and 212.233, the air and water quality must be monitored to provide assurance that the quality standards proposed elsewhere in the regulations are being met.

Sterilization (Subpart M)

The sterilization process, with its capability to destroy microorganisms, is probably the single most important process in all of LVP drug product manufacture. Therefore, an entire subpart is devoted to the details of how appropriate assurance of sterility is obtained. It enumerates the many factors to be considered in the design of the process and those required for proving that the process is uniform and consistently reproducible.

For the first time in drug CGMP regulations, FDA is establishing a process standard. This standard for the sterilization process is a lethality factor (termed F_o) of 8. For information regarding the calculation of F_o the following references, on file in the office of the Hearing Clerk, Food and Drug Administration, may be useful:

References

(1) National Canners Association, "Laboratory Manual for Food Canners and Processors," Vol. 1, Avi Publishing Co., Westport, CN, pp. 220–251, 1968.

(2) Stumbo, C. R., "Thermobacteriology in Food Processing," Academic Press, 1973.

(3) "Industrial Sterilization," Edited by Philips, G. B. and W. S. Miller, Duke University Press, Durham, NC, pp. 239–282, 1973.

(4) Pflug, I. J., "Heat Sterilization," in "Industrial Sterilization," Edited by Phillips, G. B. and W. S. Miller, Duke University Press, Durham, NC, 1973.

The survey of 1973 showed that the industry traditionally applied to its products during the sterilization process a degree of heat treatment that was minimal by today's standards and knowledge. While the extent of heating used at the time of the survey was satisfactory for

low concentrations of heat-sensitive microorganisms, the sterilization cycles employed did not provide suitable margins of safety, and there was no way to assure that some very small levels of contamination did not survive the sterilization process. Such risks are considered unnecessary in light of current sterilization technology.

Classical sterilization techniques using pure steam under pressure provided a lethality factor of 12 to 15, which has long been used as a recommended standard. However, such an amount of lethality in the form of heat may also be detrimental to the chemistry and stability of these products. After considering the process of sterilization as it applies to the production of safe and effective LVP drug products, the Commissioner believes that a manufacturing process for terminal sterilization of an LVP drug product may employ steam, mixtures of air and steam, or superheated water as the sterilizing medium, provided the procedure has been shown to deliver an F_o of 8 or more. As discussed earlier, provisions are proposed in § 212.5 for alternative facilities, equipment, processes, or control procedures and specifially in § 212.5(d) for a sterilization process delivering an F_o of less than 8.

When sterilization under conditions producing an F_o of 8 or more is coupled with all of the other control features proposed in this regulation, a generous margin of safety is provided even when fluctuations in microbial flora are encountered. The proposed F_o value of 8 has been known to be under consideration since the draft proposal was publicly released in April 1975. FDA has evidence that industry has been moving toward the establishment of more stringent sterilization processes in view of the expectation that this lethality factor would become a requirement. Some plants already employ such processes; and, therefore, the use of an F_o factor of 8 can already be considered a current good manufacturing practice.

2. Proposed § 212.243 requires that the sterilization process be tested and approved by the quality control unit. The testing of the sterlization process must include heat distribution studies and heat penetration studies.

The Commissioner believes these studies are necessary to demonstrate that the process is uniform and reproducible within certain limits. Such studies must be repeated when any changes that may affect the heat delivered to the product are made in the equipment or in the sterilization process. Heat distribution studies are necessary to document that the sterilizing medium is uniform. Heat peneration studies are performed to document that the product being sterilized is subjected to the required process standard regardless of its location in the sterilizing chamber. Sufficient studies must be performed to establish that the prescribed F_o is delivered consistently throughout the sterilizer. It is important that every manufacturer use data derived from the same processing parameters. Therefore, the Commissioner proposes that the data employed to calculate the F_o value be derived beginning when the sterilizer environment has stabilized and ending when cooling is initiated.

The Commissioner further proposes that heat penetration studies use temperature sensors, i.e., thermocouples, and suitable biological indicators as added assurance that the sterilization process is capable of microbial destruction. The indicators shall be placed in the same containers where temperature sensors are used. The Commissioner believes that biological indicators are used to some extent by all manufacturers of LVP drug products. Furthermore, the Commissioner is aware that some manufacturers use biological indicators throughout production and process development and as added assurance of sterilization in every sterilizer load. Other manufacturers, however, appear to strongly oppose such widespread use of biological indicators. The Commissioner has concluded that more information is needed before he can determine the "current good" practice of the industry and whether biological indicators in every sterilizer load are necessary to assure satisfactory sterilization. Therefore, the Commissioner requests specific comments regarding the use of biological indicators in each sterilizer load as an additional means of verifying the sterilization process. These comments, along with other information currently being developed by FDA should materially assist the Commissioner in determining the role of biological indicators in the manufacture of LVP drug products.

3. Proposed § 212.244 sets forth a number of pertinent factors that must be included in the design of a sterilization process. One of the most important of these is uniform heat distribution. If one container of an LVP drug product is to be of the same quality as any other container in the lot, then all must have been exposed to virtually the same process and have the same sterilization history. It is, therefore, proposed that the temperature of the sterilizing medium vary no more than ± 0.5 C or $\pm 1°$ F from the specified temperature once the product achieves process temperature.

Other factors such as the loading pattern of the sterilizer, the initial temperature of the product and sterilizer, venting time, product come-up time, and cooling time are discussed in this proposed section.

4. Proposed § 212.245 establishes certain controls that need to be employed during the sterilization process. Such controls include placement and periodic checking of equipment used to measure and record the temperature, times, and pressures, ensuring that bleeders on sterilizers are functioning, or assuring that water levels, where required, are maintained. Of importance in this proposed section is a determination of the microbial population and the relative heat resistance of the organism prior to sterilization. Such determination is based on samples collected at the beginning and at the end of the filling operation. There should be no evidence of significant microbial growth having occurred during the time of the filling operation nor should the microbial level or microbial heat resistance exceed those levels established during the testing and approval of the manufacturing process and control procedure. Again, this is in accordance with current good manufacturing practice.

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. The Commissioner has also carefully considered the inflation impact of the proposed regulation as required by EO 11821, OMB Circular A–107, and interim guidelines issued April 1, 1975 by the Department of Health, Education, and Welfare, and no major inflation impact has been found. Copies of the FDA environmental and inflation impact assessments are on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 501, 502, 505, 506, 507, 701, 52 Stat. 1049–1053 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 355, 356, 357, 371)) and under the authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs proposes that a new 21 CFR Part 212 be established as follows:

PART 212—CURRENT GOOD MANUFACTURING PRACTICE IN THE MANUFACTURE, PROCESSING, PACKING, OR HOLDING OF LARGE VOLUME PARENTERALS FOR HUMAN USE

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212.243 Testing of sterilization processes.
212.244 Sterilization process design.
212.245 Sterilization process controls.

AUTHORITY: Secs. 501, 502, 505, 506, 507, 701, 52 Stat. 1049–1053 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 351, 352, 355, 356, 357, 371).

Subpart A—General Provisions

§ 212.1 Scope of Part 212.

(a) The regulations set forth in Parts 210, 211, and 212 of this chapter describe the minimum current good manufacturing practice for methods to be used in, and the facilities and controls to be used for, the manufacture, processing, packing, or holding of a large volume parenteral drug product for human use, to assure that such drug product meets the requirements of the act as to safety, and has the identity, strength, quality, and plicity stated otherwise. Therefore, to is represented to possess.

(b) The regulations in this part supplement the regulations in Parts 210 and 211 of this chapter except where explicitly stated otherwise. Therefore, to determine the requirements of current good manufacturing practice for large volume parenteral drug products, the regulations in Parts 210, 211, and 212 of this chapter must be applied together. In the event it is impossible to comply with applicable regulations both in this part and in Part 211 of this chapter, the regulations in this part shall supersede the regulations in Part 211. Where requirements in this part supplement corresponding requirements in Part 211 of this chapter, the same section heading is used and is keyed numerically to the regulation in Part 211. To trace a corresponding section, refer to the last portion of the section number. For example, definitions are found in §§ 210.3, 211.3, and 212.3 of this chapter; requirements regarding responsibilities of the quality control unit are in §§ 211.22 and 212.22 of this chapter.

§ 212.3 Definitions.

(a) The terms defined in § 210.3 of this chapter have the same meaning in this part.

(b) As used in this part:

(1) "Large volume parenteral" means a terminally sterilized aqueous drug product packaged in a single-dose container with a capacity of 100 milliliters or more and intended to be administered or used in man. It includes intravenous infusions, irrigating solutions, peritoneal dialysates, and blood collecting units with anticoagulant. The term "large volume parenteral" does not include any biological drug product subject to section 351 of the Public Health Service Act (42 U.S.C. 262).

(2) "Controlled environment area" means any area in which the manufacture, processing, packing, or holding of a larger volume parenteral drug product occurs and in which environmental factors such as humidity, temperature, particulate and microbial quality of the air must be controlled to assure that the drug product has the purity characteristics that it purports or is represented to possess. Under §§ 212.29(c) and 212.81, areas in which the weighing, mixing, or filling of large volume parenteral drug products occurs, transfer areas (defined in paragraph (b)(13) of this section), and areas in which gowning occurs must be environmentally controlled. Sections 212.29, 212.42, 212.44, 212.45, 212.221, 212.223, and 212.232 establish the requirements for environmental control to be followed.

(3) "F_o" means the equivalent amount of time, in minutes at 121° C or 250° F, which has been delivered to a product by the sterilization process. The "F_o" may be calculated by several methods. One method is to integrate the time the product is exposed to heat in terms of equivalent time at 121° C or 250° F. For such calculation, a "z" value of 10° C or 18° F is assumed; the term "z" value means the slope of the thermal death time curve and may be expressed as the number of degrees Fahrenheit required to bring about a tenfold change in the death rate. A second method of determining the F_o is based on data obtained by the use of biological indicators. (For further background regarding the F_o value see "Laboratory Manual for Food Canners and Processors," Vol. 1, National Canners Association, Avi Publishing Co., Westport, CT, 1968, pp. 220–251; "Industrial Sterilization," Phillips & Miller, Duke University Press, Durham, NC, 1973, pp. 239–282; or "Thermobacteriology in Food Processing," C. R. Stumbo, Academic Press, 1973.)

(4) "HEPA filter" means a high efficiency particulate air filter with the capability of retaining 99.97 percent of particulates greater than 0.3 micron in diameter.

(5) "Heat distribution study" means a study designed to ascertain whether or not the sterilizing medium in the sterilizer is uniform during the sterilization process.

(6) "Heat penetration study" means a study designed to indicate the amount of heat received by the drug product during the sterilization process.

(7) "Laminar flow" means the movement of an entire body of air within a confined area with uniform planar velocity along parallel flow lines.

(8) "Per day" or "daily" means a time period of 24 hours on days when manufacturing processes are being performed.

(9) "Particulate matter" means mobile, undissolved substances, other than gas bubbles, unintentionally present in a large volume parenteral drug product.

(10) "Pyrogen" means a substance in a large volume parenteral drug product that can cause a febrile or fever-producing reaction in man.

(11) "Static line" means any pipe containing liquid that is not emptied or circulated at least once every 24 hours.

(12) "Sterilization process" means the application of heat to sealed containers under specific conditions of time, temperature, and pressure.

(13) "Transfer area" means any area of the manufacturing plant, other than weighing, mixing, or filling areas, where the components, in-process materials, drug products, and drug product contact surfaces of equipment, containers, and closures after final rinse of such surfaces are exposed to the plant environment.

§ 212.5 Alternative facilities, equipment, processes, or control procedures; relation to new drug applications.

(a) The regulations in this part specify some of the facilities, types of equipment, processes, and controls that must be used to obtain a desired result for the final large volume parenteral drug product. These requirements set forth what the Food and Drug Administration has found

to be the current good manufacturing practice for the manufacture, processing, packing, and holding of large volume parenteral drug products. It is not the intent of the Food and Drug Administration, however, to curtail technological advance in the form of new facilities, types of equipment, processes, or controls, where such advance accomplishes at least the results attainable by strict compliance with these regulations. Nor is it the intent to require compliance when to do so would lead to the alteration, degradation, or instability of the end product.

(b) Alternative facilities, types of equipment, processes, or controls may be used by a manufacturer if he has adequate data establishing that the alternative is equal or superior to that required in this part in terms of assuring that the large volume parenteral drug product meets the requirements of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, that it purports or is represented to possess. The burden shall be on the manufacturer to show that the alternative can deliver the same result as, or a better result than, that attained by strict compliance with these regulations.

(1) For any large volume parenteral drug product subject to section 505 of the act:

(i) The use of any such alternative described in the application or supplement approved on or before (insert effective date of final regulation) shall continue as a commitment of the holder of the application until modified pursuant to a supplemental application under § 314.8 (c) or (d) of this chapter.

(ii) The introduction of any such alternative after (insert effective date of final regulation) shall be subject to a supplemental application (including the data described in paragraph (b) of this section) under § 314.8(d) of this chapter.

(2) For any large volume parenteral drug product not subject to section 505 of the act, the use of any such alternative shall be conditioned upon the manufacturer having in his files the data described in paragraph (b) of this section and available upon request from the Food and Drug Administration.

(c) Except as provided in paragraphs (d) and (e) of this section, the requirements of this part supersede any commitments contained in a new drug application approved on or before (insert effective date of final regulation) regarding any alternative facilities, types of equipment, processes, or controls that are not equal or superior to that required in this part in terms of assuring that the large volume parenteral drug product meets the requirements of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, that it purports or is represented to possess.

(d) Any large volume parenteral drug product that would be affected, degraded, or rendered unstable in terms of its safety, identity, strength, quality or purity if made in strict compliance with the minimal sterilization process specified in § 212.240 may be processed at an F_o of less than 8 under the following conditions:

(1) There is documented evidence, including data and information, showing that the requirements of § 212.240 will affect, degrade, or render the product unstable in terms of its safety, identity, strength, quality, or purity.

(2) There is adequate data that establishes the maximum F_o that can be tolerated by the drug product.

(3) There is evidence, including results of microbiological challenge, that such alternative F_o value is adequate for the sterilization process.

(4) For large volume parenteral drug products that are subject to section 505 of the act, approval for an alternative sterilization process shall be obtained through approval of a new drug application or supplemental new drug application on or after (insert effective date of final regulation).

(5) For large volume parenteral drug products not subject to section 505 of the act, the manufacturer shall maintain for inspection under section 704 of the act any data, evidence, or other information in support of the sterilization process used in lieu of the process in § 212.240.

(e) For large volume parenteral drug product subject to section 505 of the act that would be affected, degraded, or rendered unstable in terms of its safety, identity, strength, quality or purity if made in strict compliance with the requirements of this part, other than those regarding the minimum sterilization process specified in § 212.240, shall be subject to a suplemental new drug application under § 314.8(c) of this chapter approved after (insert date of final regulation). Such application shall describe the reasons for such effect, degradation or instability; shall set forth the alternative facilities, types of equipment, processes, or controls proposed to be used, or proposed to be continued in use; and subject to a supplemental new drug apalternatives.

Subpart B—Organization and Personnel

§ 212.22 Responsibilities of quality control unit.

(a) The quality control unit shall have the responsibility and authority to test and accept or reject the design, engineering, and physical facilities of the plant, the equipment, and the manufacturing process and control procedures to be used in the manufacture, processing, packing, and holding of each large volume parenteral drug product. The quality control unit shall reject any such plant, equipment, process, or procedure if it does not comply with the provisions of this part or if, in the opinion of the quality control unit, it is not suitable or adequate to assure that the drug product has the characteristics it purports or is represented to possess.

(b) The quality control unit shall have the responsibility and authority to test and accept or reject the container-closure system, and the delivery system if attached, to be used in the manufacture, processing, packing, and holding of the intended large volume parenteral drug product. The quality control unit shall reject any such system if it does not comply with the provisions of this part, in particular the requirements of § 212.94, or if, in the opinion of the quality control unit, it is not capable of holding the product invulnerable to contamination under the intended or contemplated conditions of shipment, storage, and use.

(c) The quality control unit shall have the responsibility and authority to test and approve or reject any changes in previously approved plant, equipment, processes, procedures, and container-closures and delivery systems before utilization in the manufacture, processing, packing, and holding of a large volume parenteral drug product.

§ 212.29 Personnel responsibilities in controlled environment areas.

(a) Procedures for entering and leaving any controlled environment area shall be written. Access to a controlled environment area shall be limited to persons trained in procedures for entering, maintaining the environmental integrity of, and leaving such areas.

(b) Prior to entering a controlled environment area (other than a gowning area), personnel shall remove jewelry and unnecessary cosmetics and shall don protective gowns and footwear meeting the following standards:

(1) Gowns shall be designed appropriately to cover the head and body. Gowns may replace or cover plant uniform apparel.

(2) Gowns shall be made of nonlinting materials.

(3) Gowns may be either reuseable or disposable. If disposable, a new gown shall be donned for each entry or reentry into a controlled environment area. If reuseable, a laundered gown shall be donned for such entry or reentry.

(4) Gowns shall be clean and shall be stored and handled to minimize microbial contamination and the accumulation of particulates.

(c) Donning of gowns and footwear, and washing preparatory to entering a controlled environment area (other than a gowning area), shall be performed in specifically designated gowning areas that shall meet the requirements for a controlled environment area as defined in § 212.3(b)(2).

Subpart C—Buildings and Facilities

§ 212.42 Design and construction features.

(a) Walls, floors, ceilings, fixtures, and partitions in controlled environment areas shall:

(1) Have a smooth, cleanable finish that is impervious to water and to cleaning and santitizing solutions;

(2) Be constructed of materials that resist chipping, flaking, oxidizing, or other deterioration.

(b) Floors that are cleaned by flooding or floors that are in areas where operations discharge water or liquid product waste onto the floor shall be curved (coved) at the floor-wall junction. Floors

shall be sloped to a drain and sealed to facilitate cleaning.

(c) There shall not be horizontal fixed pipes or conduits over exposed components, in-process materials, drug products, and drug product contact surfaces, including drug product containers and closures after the final rinse.

(d) In each physically separated area, pipes or conduits for air or liquids shall be identified as to their contents. Such identification shall be by name, color code, or other suitable means.

§ 212.43 Sterilization areas.

Sterilization areas shall be designed and equipped to prevent intermingling of sterilized and unsterilized material or drug products.

§ 212.44 Lighting.

Lighting fixtures in controlled environment areas shall:

(a) Be constructed in a manner to prevent any accumulation of dust and to facilitate cleaning.

(b) Be covered to prevent scattering of any material in case of breakage.

§ 212.45 Gowning area.

There shall be a gowning area that is:

(a) Located immediately adjacent to the controlled environment work areas served;

(b) Supplied with air so that the area has a negative air pressure relative to any controlled environment work area served and has a positive air pressure relative to the atmosphere and to any adjacent noncontrolled environment area; the requirements for air in controlled environment areas are found in § 212.221. The air pressure differential shall be monitored;

(c) The sole means of personnel entry and exit at each controlled environment work area served, except for emergencies;

(d) Equipped with receptacles for disposal of used garments;

(e) Equipped with surgical type handwashing facilities and warm-air handdrying equipment.

§ 212.47 Compressed air.

Each building shall include a compressed-air processing and distribution system capable of supplying compressed air meeting the requirements of § 212.223 to sites where needed.

§ 212.49 Water and other liquid-handling systems.

(a) Filters may not be used at any point in the water for manufacturing or final rinse piping system.

(b) Backflow of liquids shall be prevented at points of interconnection of different systems.

(c) Pipelines for the transmission of water for manufacturing or final rinse and other liquid components shall:

(1) Be constructed of welded stainless steel (nonrusting grade) equipped for sterilization with steam, except that sanitary stainless steel lines with fittings capable of disassembly may be immediately adjacent to the equipment or valves that must be removed from the lines for servicing and replacement.

(2) Be sloped to provide for complete drainage.

(3) Not have an unused portion greater in length than six diameters of the unused pipe measured from the axis of the pipe in use.

(d) Pipelines for the transmission of liquid in-process materials and drug products shall meet the requirements of paragraph (c) of this section except that pipelines capable of disassembly for manual cleaning may be used in lieu of the requirements of paragraph (c)(1) of this section.

§ 212.51 Production waste liquids.

(a) Drainage systems for production waste liquids shall not be utilized for sanitary waste. A means to prevent backflow of sanitary wastes into the process waste lines shall be provided and shall be located outside of the immediate building where production occurs.

(b) Waste liquids shall be introduced to sewers through trapped drains. Drains from equipment shall be designed with an atmospheric break to prevent backsiphonage.

Subpart D—Equipment

§ 212.63 Equipment design, size, and location.

Equipment such as guide rails, diverters, and transfer mechanisms that contact glass bottles shall be designed to prevent damage, i.e., breakage, cracking, or chipping, to the bottles.

§ 212.65 Equipment construction.

Equipment shall be constructed so that surfaces that contact components, in-process materials, drug products, or the drug product contact area of containers or closures shall not affect the safety, identity, strength, quality, or purity of the large volume parenteral drug product.

§ 212.67 Equipment cleaning and maintenance.

The following requirements shall be included in written procedures and cleaning schedules:

(a) All equipment and surfaces that contact components, in-process materials, drug products, or drug product contact surfaces such as containers and closures shall be cleaned and rinsed with water meeting the quality requirements stated in § 212.224.

(b) Immediately prior to such contact, equipment and surfaces specified in paragraph (a) of this section shall be given a final rinse with water meeting the quality requirements stated in § 212.225.

(c) Steam used to sterilize liquid-handling systems or equipment shall be free of additives used for boiler control.

(d) Procedures for maintaining and cleaning dust-removal systems shall prevent the dispersion of dust into the plant environment.

§ 212.68 Equipment calibration.

(a) Procedures shall be written and followed designating schedules and assigning responsibility for testing or monitoring the performance or accuracy of automatic or continuously operating equipment, devices, apparatus, or mechanisms such as, but not limited to, the following:

(1) Alarms and controls on sterilizing equipment.

(2) Temperature-recording devices on sterilizers.

(3) Pressure gauges.

(4) Mechanisms for maintaining sterilizing medium uniformity.

(5) Chain speed recorder.

(6) Heat exchanger pressure differential monitor.

(7) Mercury-in-glass therometer.

(b) Written records of such calibrations, checks, examinations, or inspections shall be maintained, as specified in § 212.183.

§ 212.72 Filters.

(a) The integrity of all air filters shall be verified upon installation and maintained throughout use. A written testing program adequate to monitor integrity of filters shall be established and followed. Results shall be recorded and maintained as specified in § 212.183.

(b) Solution filters shall be sterilized and installed aseptically. The integrity of solution filters shall be verified by an appropriate test, both prior to any large volume parenteral solution filtering operation and at the conclusion of such operation before the filters are discarded. If the filter assembly fails the test at the conclusion of the filtering operation, all materials filtered through it during that filtering operation shall be rejected. Rejected materials may be refiltered using filters whose integrity has been verified provided that the additional time required for refiltration does not result in a total process time that exceeds the limitations specified in § 212.111. Results of each test shall be recorded and maintained as required in § 212.188(e).

§ 212.73 Sterilizers employing steam or air-steam mixtures.

Sterilizers employing steam or air-steam mixtures shall include the following features:

(a) *Mercury-in-glass thermometer.* Each sterilizer shall be equipped with at least one mercury-in-glass thermometer of known accuracy having a temperature range that spans not more than 56° C or 100° F in the processing range on a scale at least 18 centimeters or 7 inches in length. The scale divisions shall be in increments of no more than 1° C or 2° F. These thermometers shall be installed where they can be accurately and easily read. Bulbs of thermometers shall be installed either within the sterilizer shell or in external wells attached to the sterilizer. External wells or pipes shall be connected to the sterilizer through at least a ¾-inch diameter opening, and shall be equipped with a 1/16-inch or larger bleeder opening located to provide a full flow of the sterilizing medium past the length of the thermometer bulb.

(b) *Temperature-recording device.* Each sterilizer shall be equipped with an

accurate temperature-recording device adjusted to agree within 0.5° C or 1° F of a known accurate mercury-in-glass thermometer. A means of preventing unauthorized changes in adjustment shall be provided. The chart graduations shall not exceed 1° C or 2° F within a range of 5° C or 10° F of the processing temperature. Each chart shall have a working scale of not more than 30° C or 50° F per inch within a range of 10° C or 20° F of the processing temperature. This recorder may be a recording-controlling instrument. The temperature recorder sensor shall have a response time not greater than 2 seconds for a 90 percent scale response. The temperature recorder sensor shall be installed either within the sterilizer shell or in a well attached to the shell, located to provide a full flow of the sterilizing medium past the length of the recorder sensor. External wells or pipes shall be connected to the sterilizer through at least a ¾-inch diameter opening, and shall be equipped with a 1/16-inch or larger bleeder opening.

(c) *Pressure gauges.* Each sterilizer shall be equipped with a pressure gauge having a scale graduated in increments of no more than 2 pounds per square inch of mercury (psig). All pressure gauges shall be equipped with a watertight pressure-transmitting diaphragm unless the gauge is connected directly to the sterilizer, or a connecting line by a straight, self-draining pipe or tube no more than 10 centimeters or 4 inches in length.

(d) *Air and steam controls.* (1) Each sterilizer shall be equipped with a steam controller to maintain the sterilizer temperature.

(2) The steam controller shall be designed to be activated by temperature variation rather than by pressure variation, and shall be designed to prevent unauthorized changes.

(3) The steam controller may be combined with a recording thermometer. For sterilizers using air-steam mixtures, there shall be mechanisms capable of establishing and maintaining the degree of temperature uniformity required for the sterilization process, the testing of which is required in § 212.243, and a means of automatically controlling and recording the ratio of air and steam introduced into the vessel so that the prescribed air-steam ratio is maintained.

(e) *Steam introduction.* Steam may enter either the top or bottom of the sterilizer. The steam inlet shall be located in that portion of the sterilizer opposite the vent and shall be large enough to provide sufficient steam for proper operation of the sterilizer.

(f) *Steam and air-steam distribution.* The distribution of steam or an air-steam mixture in the sterilizer shall be accomplished in a manner adequate to provide uniform heat distribution throughout the sterilizer. Steam spreader pipes from the steam line inside the sterilizer shall, individually, be no larger than the steam inlet line. Steam spreaders shall extend along the length of the sterilizer. The perforations shall be along a 90° sector of the spreader and shall direct steam toward the central longitudinal axis of the sterilizer. Horizontal steam sterilizers over 30 feet long shall have at least two steam inlets connected to the spreader. The total cross-sectional area of the perforations shall be equal to 1½ to 2 times the cross-sectional area of the steam inlet line. Any mechanical device utilized to maintain uniformity of the sterilizing medium within the sterilizer shall be equipped with both audio and visual alarms to signal improper operation.

(g) *Bleeders.* Bleeders, except those for thermometer and temperature recorder sensor wells, shall be ⅛ inch or larger. Bleeders shall be located within approximately 1 foot of each end of the sterilizer. At least one bleeder shall be located so that the operator can observe whether bleeders are functioning properly during processing.

(h) *Air overpressure.* The sterilizer shall be supplied with a source of compressed air meeting the requirements of § 212.223. The sterilizer shall have a mechanism to ensure that overpressure is established before cooling begins and a means of controlling the overpressure within established limits.

(i) *Water level controls and indicator.* The sterilizer shall be equipped with an apparatus to control the level of water within the sterilizer so that the water does not come into contact with the lowest container in the vessel. The apparatus shall be so constructed that when a predetermined water level is reached, it automatically opens a drain valve. There shall be an audio and visual alarm system, independent of the water-level controlling apparatus, which is activated if the water exceeds the predetermined level. There shall be a visual means of observing the water level in the sterilizer during its operation.

(j) *Vents.* Vents shall be installed so that before they are closed all air is removed from steam sterilizers and excess air is removed from sterilizers employing air-steam mixtures. Vents shall be controlled by gate, plug cock, or other suitable types of valves that can be fully opened to permit rapid discharge of air from the sterilizer during the venting period. Vents shall not be connected directly to a closed drainage system without an atmospheric break. If an overflow pipe is used as a vent, there shall be an atmospheric break in the line before it connects to a closed drain. Where several vent pipes from a single sterilizer are connected to a manifold, venting through the manifold shall be controlled by a gate, plug cock, or other suitable type of valve that can be fully opened to permit rapid discharge of air from the sterilizer during the venting period. The cross-sectional area of the manifold shall be larger than the total cross-sectional area of all connecting vent pipes. The manifold shall not be directly connected to a closed drain without an atmospheric break in the line. A header connecting vent pipes or manifolds from several sterilizers shall lead to the atmosphere, and the venting shall be controlled by valves in the manifold or vent pipes for each sterilizer. The header shall not be controlled by a valve and shall be of such a size that the cross-sectional area of the header is at least equal to the total cross-sectional area of all connecting vent or manifold pipes from all sterilizers venting simultaneously.

(k) *Drain valves.* A nonclogging watertight valve such as a ball or plug type shall be used. Screens shall be installed over all drain openings.

(l) *Cooling equipment.* (1) Sterilizers using air, as referred to in § 212.223, for pressure cooling shall be equipped with a ball or gate valve or suitable valve and piping arrangement on the air line to prevent air leakage into the sterilizer during processing.

(2) Lines transmitting water (the requirements for which are stated in § 212.226) to the sterilizer for cooling the drug product after sterilization, including any connected heat exchangers, shall be designed so they can be drained and sterilized. They shall provide a separate loop for each sterilizer. The system shall include a means for treating the cooling water to eliminate microorganisms; however, filtration shall not be used as a means for such treatment. The cooling lines shall not be connected to a drain without an atmospheric break. Interconnections between water cooling systems and all other systems, such as compressed air, shall be designed with a means of preventing backflow. A pump may be used for circulating cooling water. Any additional cooling water added to the circulating water shall be introduced into the suction side of the pump.

§ 212.74 Sterilizers employing superheated water.

Sterilizers employing superheated water shall conform to the requirements of § 212.73(a), (b), (c), (j), (k), and (l) and shall include the following additional features:

(a) *Steam introduction.* In horizontal sterilizers the steam distributor shall extend the length of the bottom of the sterilizer with perforations distributed uniformly along the upper part of the pipe.

(b) *Water quality.* The water used in this sterilization process shall meet the requirements of § 212.224.

(c) *Water level controls and indicator.* There shall be an automatic method of controlling water level to assure that all containers are covered, and it shall be provided with an audio and visual alarm system to signal any malfunction. There shall be a means of observing the water level in the sterilizer during its operation.

(d) *Air supply and controls.* A means shall be provided for introducing compressed air, as described in § 212.223, at the proper pressure and rate. The pressure shall be controlled by an automatic pressure control unit. If compressed air is used to promote circulation, it shall be introduced into the steam line at a point between the sterilizer and the steam control valve at the bottom of the sterilizer.

(e) *Water circulation.* When a water circulation system is used for heat distribution, it shall be installed in such a manner that water will be drawn from the bottom of the sterilizer through a suction manifold and discharged through a spreader that extends the length of the top of the sterilizer. The holes in the water spreader shall be uniformly distributed and shall have an aggregate area not greater than the cross-sectional area of the outlet line from the pump. The suction outlets shall be protected with nonclogging screens to keep debris from entering the circulation system. The pump shall be equipped with a bleeder to remove air when starting operations and with an audio and visual alarm system to signal any malfunction.

(f) *Cooling water supply.* The water, as described in § 212.226, used to cool the drug product after sterilization shall be introduced at the top of the sterilizer and above the top of the containers. If cooling is done by complete submersion of the containers, the water for cooling shall be introduced below the water level.

§ 212.75 Hydrostatic sterilizers employing steam under pressure.

Hydrostatic sterilizers employing steam under pressure shall conform to the requirements of § 212.73(c), (d), (i), (j), (k), and (l) and shall include the following additional features:

(a) *Mercury-in-glass thermometer.* Each sterilizer shall be equipped with at least one mercury-in-glass thermometer with a temperature range of not more than 56° C or 100° F in the processing range on a scale at least 18 centimeters or 7 inches in length. The mercury-in-glass thermometers shall be located near the bottom automatic recorder so that they can be accurately and easily read.

(b) *Temperature recorder device.* Each sterilizer shall be equipped with an accurate temperature-recording device adjusted to agree within 0.5° C or 1° F of a known accurate mercury-in-glass thermometer. A means of preventing unauthorized changes in adjustment shall be provided. The chart graduations shall not exceed 1° C or 2° F within a range of 5° C or 10° F of the processing temperature. Each chart shall have a working scale of not more than 30° C or 50° F per inch within a range of 10° C or 20° F of the processing temperature. The temperature recorder sensor shall have a response time not greater than 2 seconds for a 90 percent scale response and may be installed either within the steam dome or in a well attached to the dome. Sensor wells shall have a 1/16-inch or larger bleeder opening emitting steam continuously during the entire processing period. Additional sensors shall be installed in the hydrostatic water legs if the sterilization process specifies maintenance of particular temperatures in the hydrostatic water legs.

(c) *Steam introduction.* Steam may enter either to top or bottom of the steam dome of the sterilizer. The steam inlet shall be located in that portion of the sterilizer opposite the vent and shall be large enough to provide sufficient steam for proper operation of the sterilizer.

(d) *Bleeders.* Bleeder openings 1/4 inch or larger shall be located in the steam dome opposite from the point of steam entry.

(e) *Chain speed.* The sterilizer shall be equipped with an automatic device that will stop the product container conveyor chain when the dome temperature drops below that specified in the sterilization process. A means of preventing unauthorized speed changes and a means of recording speeds shall be provided.

§ 212.76 Heat exchangers.

Heat exchangers, other than the welded double-concentric-tube type or double-tube sheet type, must employ a pressure differential and a means for monitoring the differential. The pressure differential shall be such that the fluid requiring a higher microbial quality shall be that with the greater pressure. Written records of the pressure differential monitoring shall be maintained as required in § 212.183.

§ 212.77 Laminar flow control equipment.

Equipment at the filling line and microbiological testing area shall provide HEPA-filtered laminar flow air. Such equipment shall:

(a) Have hood or air flow direction panels and working surface areas that are constructed of a smooth, durable, nonflaking material such as glass, plastic, or stainless steel.

(b) Have prefilters that are disposable or fabricated from a material that can be properly cleaned and reused.

(c) Have HEPA final filters that have been tested to assure leak proof construction and installation.

(d) Provide a laminar air flow with an average velocity of 90 feet per minute over the entire air exit area. The velocity shall not drop below 75 or exceed 105 feet per minute at any point.

(e) Provide shadowless illumination with a minimum intensity of 100 foot-candles at the working level.

(f) Be in operation for at least 15 minutes before beginning filling or microbial-testing operations.

(g) Be monitored according to a written program and schedule for compliance with the requirements of paragraphs (c), (d), and (e) of this section and as stated in § 212.231. Written records shall be maintained of all test results and any corrective measures taken, as required in § 212.183.

§ 212.78 Air vents.

All stills and tanks holding liquid requiring microbial control shall have air vents with non-fiber-releasing sterilizable filters capable of preventing microbial contamination of the contents. Such filters shall be designed and installed so that they do not become wet. Filters shall be sterilized and installed aseptically. Tanks requiring air vents with filters include those holding water for manufacturing or final rinsing, water for cooling the drug product after sterilization, liquid components, and in-process solutions.

§ 212.79 Pumps.

Pumps moving water for manufacturing or final rinsing, water for cooling the drug product after sterilization, and in-process or drug product solutions shall be designed to utilize water for injection as a lubricant for the seals.

Supart E—Control of Components, Drug Product Containers, Closures, and In-Process Materials

§ 212.81 Operations requiring controlled environment.

The weighing, mixing, or filling of large volume parenteral drug products and transfer operations, as described in § 212.3(b)(13), shall be performed in specifically designated areas that shall meet the requirements for a controlled environment area as defined in § 212.3(b)(2).

§ 212.84 Testing and approval or rejection of components, drug product containers, and closures.

(a) Representative samples of all components, even though not generally considered liable to microbiological contamination, shall be periodically subjected to microbiological examinations on a scheduled basis according to a written program. Components shall not contain heat resistant spores or other microbiological contaminants that are objectionable in view of the use of the component and the manufacturing process to which it will be subjected. Component specifications shall include microbiological limits based on data that have been obtained from the periodical microbiological testing program. Such limits shall be approved by the quality control unit as part of component specifications.

(b) Representative samples of each shipment of each manufacturer's lot of components, drug product containers, and closures shall be tested for pyrogenic properties prior to release by the quality control unit for use in production, as required in § 212.167(a). Those lots that do not conform to established specifications shall be rejected. Rejected lots of components, containers, and closures may be reprocessed to remove the pyrogenic properties provided there is assurance that the reprocessed material will meet appropriate standards, specifications and characteristics.

(c) Water used as a component shall meet the requirements of § 212.225 of this part.

§ 212.94 Drug product containers and closures.

(a) The quality control unit shall test the drug product container-closure system to be employed for a large volume parenteral drug product, and the delivery system if attached, by chemical and physical tests and biological challenges to determine whether it is capable of holding the product invulnerable to contamination under the intended or contemplated conditions of shipment, stor-

age, and use. Any such system that is found incapable of so holding the product shall not be used. Written records of all testing under this paragraph shall be maintained as required in § 212.180.

(b) Each shipment of each lot of containers and closures shall be sampled and tested for physical characteristics according to a statistically valid sampling plan. Samples shall be examined by the quality control unit. If the reliability of the supplier has not been established or if the physical characteristics of containers or closures are changed, 100 percent inspection for physical defects shall be conducted until adequate data are collected to demonstrate the assurance of quality of these articles.

(1) When 100 percent inspection is performed, it shall be followed by the selection of a representative sample drawn according to a statistically valid sampling plan. This sample shall be examined by the quality control unit. If the results are satisfactory to the quality control unit, the lot may be approved for use.

(2) If the results of the examination of the statistically drawn sample are not satisfactory to the quality control unit, the lot shall be rejected. Additional 100 percent reinspections of the lot may be performed as long as each one is followed by the selection of another statistically valid sample and examination by the quality control unit.

(c) A drug product container or closure shall not be used in the packaging of a drug product unless cleaned and initially rinsed with water meeting the requirements of § 212.224 and finally rinsed with water meeting the requirements of § 212.225.

Subpart F—Production and Process Controls

§ 212.100 Written procedures; deviations.

(a) The quality control unit shall test the manufacturing processes and control procedures to be used in the manufacture, processing, packing, and holding of a large volume parenteral drug product to determine whether they comply with the provisions of this part and are otherwise adequate to assure that the drug product has the characteristics it purports or is represented to possess. Any process or procedure that is found not to so comply or not to be so adequate shall not be utilized. Written records of all testing under this paragraph shall be maintained, as required in § 212.180.

(b) Written procedures shall be established, and shall be followed. Such procedures shall:

(1) Ensure that all static lines are flushed prior to use. Such procedures shall require that flushing produce a turbulent flow for 5 minutes and that all valves on the line are opened and closed repeatedly to flush the valve interior.

(2) Describe the action to be taken with regard to the drug product in the sterilizer if the automatic controls fail or the alarm systems signal a malfunction during sterilization operations.

§ 212.104 Accounting for losses in manufacturing.

Losses occuring in the manufacture of each batch, such as those due to breakage, improper fill volumes, in-process tests, and loss of bulk solution employed to flush solution lines and filling equipment, shall be identified, estimated in amount, and recorded.

§ 212.105 Equipment identification.

All sterilizer baskets, trucks, carts, crates, or any other contrivance used to hold a drug product during the sterilization process shall:

(a) Be plainly and conspicuously marked with a heat-sensitive indicator or other effective means to visually indicate whether or not they have been exposed to the sterilization process; and

(b) Be identified as to batch and lot. Such identification shall be retained in the batch production records, described in § 212.188.

§ 212.110 Sampling of in-process materials and drug products.

(a) Written procedures and schedules shall be established for statistically valid sampling and testing to include the following:

(1) Adequacy of mixing prior to filling.

(2) Identity and strength of the product.

(3) Levels of fill (net content).

(4) Vacuum, where applicable, or other indices of closure tightness.

(5) Solution clarity.

(6) pH.

(7) Microbial population.

(8) Pyrogenicity.

(9) Particulate matter.

(b) In-process materials and drug products not meeting established specifications shall be rejected.

§ 212.111 Time limitations on production.

The time elapsing between the addition of water for manufacturing (product make-up water) to the mixing tank and the exposure of the last unit filled to the start of sterilization cycle may not exceed 8 hours.

§ 212.116 Filtration.

(a) Prior to filling, large volume parenteral drug products shall be filtered through systems having a final mean porosity of no more than 0.45 micron; except, however, a final filter with a mean porosity of greater than 0.45 micron may be used for viscous products if necessary to provide a flow rate that will keep the production time in conformity with § 212.111. When it is necessary to use a filter with a porosity of greater than 0.45 micron because of solution viscosity, such filter shall be the minimum porosity that will provide a flow rate to keep production time in conformity with § 212.111.

(b) Final filtration of solutions shall be performed immediately prior to filling. Process specifications shall indicate the maximum time during which a filtration system may be used. Such time length shall preclude microbial build-up to levels that may affect the biological quality of the large volume parenteral, and in no case shall it exceed 8 hours.

(c) Filters shall be tested as specified in § 212.72.

§ 212.117 Drug product inspection for particulate matter.

(a) All large volume parenteral drug products shall be visually examined for particulate matter against black and white backgrounds after sterilization. The source and direction of light should enhance the visibility of particulate matter. An alternate method of examination may be employed if data are available that demonstrate that the alternate method is at least as sensitive and accurate as the visual examination.

(b) Any drug product found to contain visual particulate matter shall be rejected.

(c) Records of the examination performed shall be maintained as specified in § 212.188(i).

§ 212.118 Reuse of sterilized glass.

Written procedures shall be established and followed for the reuse of glass that has previously been subjected to the sterilization process. Such procedures shall include:

(a) Data from studies performed showing the effect of repeated sterilization upon the capability of the containers to meet all established specifications;

(b) The number of times that any drug product container may be subjected to sterilization processes;

(c) Written records as specified in § 212.184.

Subpart G—Packaging and Labeling Control

§ 212.130 Packaging and labeling operations.

The materials employed to package large volume parenteral drug products for shipment shall be adequate to protect the containers and container-closure systems from damage during customary conditions of shipment and handling.

Subpart H—Holding and Distribution

§ 212.142 Warehousing procedures.

The written procedures describing warehousing of large volume parenteral drug products shall include specific directions concerning stacking of cases so that storage does not jeopardize the identity, strength, quality, or purity of the drug product.

§ 212.150 Distribution procedures.

Written procedures that provide for proper handling of large volume parenteral drug products during shipment shall be established and followed. The services of any carriers who are found routinely to handle large volume parenteral drug products in a manner that may affect the identity, strength, quality or purity of these drug products shall be discontinued.

Subpart I—Laboratory Controls

§ 212.167 Special testing requirements.

(a) For each batch of a large volume parenteral drug product and prior to sterilization, there shall be laboratory

testing to determine whether or not it meets the requirements for the absence of pyrogens when tested according to the method prescribed in the U.S.P. An alternate test method may be employed provided that data are available to demonstrate that the alternate method is as sensitive and accurate as the U.S.P. method.

(1) Containers from among the first and last containers filled in a batch shall be examined for pyrogens.

(2) A pyrogen test shall be performed on the first container filled following any significant stoppage during filling, e.g., when filters are changed.

(3) Samples for pyrogen testing may be combined or pooled only when the quantity of material in a container does not provide sufficient material with which to perform the test.

(b) For each lot of large volume parenteral drug product there shall be laboratory testing of filled containers after sterilization to determine the degree of contamination with particulate matter. The sampling and testing conducted shall be sufficient to assure that the entire lot conforms to standards specified in the U.S.P. for particulate matter in large volume injections for single-dose infusion drug products. Alternative methodology may be used if data are available to demonstrate that the alternative method is equivalent to the U.S.P. method.

(c) For each lot of large volume parenteral drug product there shall be laboratory testing for sterility of filled containers after sterilization. The test procedures for membrane filtration specified in the U.S.P. or an equivalent sterility testing method shall be used.

(d) HEPA laminar flow hoods meeting the specifications of §§ 212.77 and 212.222 shall be used in the performance of microbiological tests.

Subpart J—Records and Reports

§ 212.180 General requirements.

Records documenting the testing by, and approval of, the quality control unit regarding the design, engineering, and physical facilities of the plant, the equipment, process and control procedures, and the container-closure systems used in the manufacture, processing, packing, and holding of a large volume parenteral drug product, shall be available for inspection at the establishment where such manufacture, processing, packing, or holding occurs. Such records shall be maintained for at least 2 years after the expiration date of each batch of drug product manufactured, processed, packed, or held in such plant, by such equipment, process or procedure, or with such container-closure system.

§ 212.182 Equipment cleaning and use log.

(a) Written records of the corrective action taken pursuant to §§ 212.224 (a) and (c), and 212.225 (a) and (b), including validation of the effectiveness of the action, shall be maintained.

(b) Written records of equipment usage shall include documentation of the length of time the equipment was in use as indicated in § 212.111.

(c) Written records demonstrating a positive pressure differential, as described in and required by § 212.76, shall be maintained.

(d) For hydrostatic sterilizers, written records of usage shall also contain the chain speed chart as indicated by § 212.245(h) and the temperature charts for the various portions as indicated by § 212.245(g) identified with the names and lot numbers of material processed.

(e) For filtration equipment or devices, written records documenting the installation, replacement, and sterilization (where appropriate) of filters such as those indicated in §§ 212.72, 212.77(b) and (c), 212.78, and 212.222(a) shall be maintained.

§ 212.183 Equipment calibration and monitoring records.

Written records of calibration and monitoring tests and readings performed shall be maintained for at least 2 years after the expiration date of each batch of drug product produced by the equipment.

(a) Calibration records shall include:

(1) A description of the equipment.

(2) The date the equipment was purchased.

(3) The operating limits of the equipment.

(4) The date, time, and type of each test.

(5) The results of each test.

(6) The signature of each person performing a test.

(7) The date the equipment was installed.

(b) Monitoring records shall include:

(1) A description of the equipment.

(2) The date the equipment was installed.

(3) The date the equipment was last calibrated, if appropriate.

(4) The operating limits of the equipment.

(5) The date and time of the recording.

(6) The reading.

(7) The signature of each person performing the monitoring.

(c) Corrective measures employed to bring the equipment into compliance with its operating specifications shall be:

(1) Recorded in the appropriate equipment log.

(2) Noted in the calibration and/or monitoring record.

(3) Immediately followed by testing to assure that the corrective measures were adequate to restore the required operating characteristics.

§ 212.184 Component, drug product container, closure, and labeling records.

Inventory records of any reused component, container, closure, or in-process material shall be maintained. Such records shall include the results of any examination or testing performed to determine the acceptability of any such article for reuse.

§ 212.188 Batch production and control records.

These records shall include the following information where appropriate:

(a) Time and temperature data from the sterilization process employed, as indicated by §§ 212.73 (a) and (b), 212.74, 212.75 (a) and (b), and 212.245 (d) and (g), identified with the date and batch number of large volume parenteral produced.

(b) Data produced when an air-steam mixture is the sterilizing medium as indicated by § 212.73(d).

(c) Documentation that overpressure was established prior to the initiation of cooling and maintained as indicated in §§ 212.73(h) and 212.74(d).

(d) Records of the sterilizer chain speed as indicated in §§ 212.75(e) and 212.245(h), identified with the date and the batch number of the material processed.

(e) Data from tests or checks made to show that the filter assembly was intact as indicated in § 212.72(b).

(f) The amount of time elapsed for significant phases of production as indicated in § 212.111.

(g) Information indicating what portion of a batch was sterilized in a specific sterilizer, along with the identification used on each basket, truck, cart, crate or other contrivance used to hold the drug product during the sterilization process as indicated in § 212.105.

(h) The results and data from in-process tests as performed in accordance with § 212.110.

(i) The number of units inspected, rejected, and accepted, and the classification of the defects causing rejection such as indicated in § 212.117.

(j) The quantities of reused components, drug product containers, and closures, or in-process materials used in the manufacture of a batch.

(k) The results of the aerobic plate counts and relative heat resistance tests as indicated in § 212.245(e).

(l) Verification that static lines were flushed prior to use according to established written procedures in § 212.100(b).

(m) Complete information on the action taken if automatic sterilizer controls fail or alarms are activated during sterilization of a batch as indicated in § 212.100(b).

(n) The results of checks made to determine that bleeders are operating satisfactorily during the sterilization of a batch as required in § 212.245(c).

§ 212.190 Air and water monitoring records.

Written records of the air and water monitoring test results, readings, and corrective measures taken shall be maintained for at least 2 years after the expiration date of each batch of drug product produced in the area being monitored or containing the water as a component.

The record shall include, at a minimum, the following information:

(a) Identity of the material being monitored.

(b) Each characteristic being monitored.
(c) Each specification limit.
(d) Each testing method used.
(e) Site sampled or monitored.
(f) The date and time of each monitoring or testing.
(g) The result of each test or monitoring reading.
(h) Batch number and expiration date of the drug product being processed in the area or equipment, or to which the component is being added at the time of monitoring or sampling.
(i) Corrective measures employed to bring the area, component or product into compliance with specifications.
(j) Retesting results to verify the adequacy of the corrective measures.

§ 212.192 Production record review.

The review and approval of production and control records by the quality control unit shall extend to those records not directly related to the manufacture, processing, packing, or holding of a specific batch of large volume parenteral drug product but which have a bearing on the quality of batches being produced. Such indirectly related records shall include:
(a) Those dealing with equipment calibration or standardization.
(b) Those demonstrating control of the sterilization process.
(c) Those demonstrating the quality of water produced by various processing systems.
(d) Those demonstrating the quality of air produced by various systems.

Subpart K—[Reserved]

Subpart L—Air and Water Quality

§ 212.220 General requirements.

(a) Air or water as described in this part may not be used until the plant, processes, and procedures used in producing and distributing it have been tested and approved by the quality control unit as capable of consistently producing air or water meeting the requirements set forth in this subpart.
(b) In addition to the requirements of this subpart, air and water quality shall be monitored as specified in Subpart J.
(c) The results of all testing and data generated shall be recorded and maintained as required by § 212.180.
(d) Procedures designating schedules, assigning responsibility, and describing in detail the action to be taken to assure that the systems produce and deliver air and water that conform to the requirements set forth in this subpart shall be written. Such procedures shall also specify the corrective action to be taken when testing reveals that the established standards are not being met. Records of corrective actions shall be maintained, as specified in § 212.190.

§ 212.221 Air in controlled environment areas.

Air in controlled environment areas shall have:
(a) A per-cubic-foot particle count of not more than 100,000 in a size range of 0.5 micron and larger when measured with automatic counters, or 700 particles in a size range of 5.0 microns or larger when measured by a manual microscopic method.
(b) A temperature of 72° F±5° or 22° C±3°.
(c) A maximum relative humidity of 50 percent and a minimum of 30 percent.
(d) A positive pressure differential of at least 0.05 inch of water with all doors closed in relation to less clean adjacent areas.
(e) At least 20 air changes per hour.

§ 212.222 Air over filling lines and at microbiological testing sites.

Air over filling lines and at microbiological testing sites shall:
(a) Have a per-cubic-foot particle count of not more than 100 in a size range of 0.5 micron and larger throughout the entire work area upstream of the work piece.
(b) Be supplied at the point of use as specified in § 212.77.

§ 212.223 Compressed air.

Compressed air used in manufacturing and processing operations, including the sterilization process, shall be:
(a) Filtered at points of use to meet the requirements of the area:
(1) Compressed air to be used in the sterilizer after the sterilization process shall meet the requirements of § 212.222 (a) for particle count and size.
(2) Compressed air to be used at the filling line or microbiological testing area shall meet the requirements of § 212.222(a) for particle count and size.
(3) Compressed air to be used in controlled environment areas shall meet the requirements of § 212.221(a) for particle count and size.
(b) Supplied by an oil-free compressor and be free of oil and oil vapor unless vented directly to a noncontrolled environment area.
(c) Dehumidified to prevent condensation of water vapor in the pipes.

§ 212.224 Water for cleaning or initial rinsing.

Water used to cleanse or initially rinse drug product contact surfaces such as containers, closures, and equipment shall:
(a) Meet the standards prescribed in the Public Health Service Drinking Water Standards set forth in Subpart J of 42 CFR Part 72;
(b) Be subjected to a process such as chlorination for control of microbial population;
(c) Contain not more than 50 microorganisms per 100 milliliters in three consecutive samples from the same sampling site when tested by the method specified in § 212.225(b) after neutralizing bacteriocidal agents, if present.

§ 212.225 Water for manufacturing or final rinsing.

Water used as a component or as a final rinse for equipment or product contact surfaces shall:
(a) Conform to the specifications in the U.S.P. for "Water for Injection":
(b) Contain not more than 10 microorganisms per 100 milliliters in three consecutive samples from the same site when samples of 250 milliliters or more are tested for total aerobic count by the plate method set forth in Microbial Limit Tests in the current revision of the U.S.P. Alternate methodology may be used provided that data are available to demonstrate that the alternate method is equivalent to the official method. When the microbial quality falls below that specified in this section, use of such water shall cease, and corrective action shall be taken to clean and sterilize the system so that the water conforms to the limit.
(c) Be stored in a suitable vessel or system including a piping network for distribution to points of use:
(1) At a temperature of at least 80° C under continuous circulation, or
(2) At ambient or lower temperatures for not longer than 24 hours, after which time such water shall be discarded to drain.

§ 212.226 Water for drug product cooling.

Water used in the sterilizer as a drug product cooling medium shall:
(a) Be treated to eliminate microorganisms;
(b) Contain not more than one microorganism per 100 milliliters in three consecutive samples from the same sampling site when one liter or more are tested for total aerobic count by a membrane filtration method and placing each membrane filter on appropriate nutrient media after neutralizing any bacteriocidal agents present in the water samples.

§ 212.227 Boiler feed water.

Feed water for boilers supplying steam that contacts components, in-process materials, drug products, and drug product contact surfaces shall not contain volatile additives such as amines or hydrazines.

§ 212.231 Monitoring of air and water quality.

(a) After the plant, equipment, manufacturing processes, and control procedures have been tested and approved by the quality control unit, there shall be performed in accordance with written procedures and schedules a sampling and testing program that is designed to monitor the microbial flora of the plant and its environment. The design of the sampling and testing program shall include monitoring of air and water quality in accordance with requirements set forth in this subpart and taking corrective action when such requirements are not met.
(b) If the results of any one sample of air or water exceed the quality limits specified in this subpart, more frequent sampling and testing shall be required to determine the need for corrective action.
(c) Representative colonies of microorganisms found by the monitoring required in this section shall be identified by genus. The colonies shall be quantified.
(d) Written records of all test findings and any resultant corrective measures

taken shall be maintained, as specified in § 212.190.

§ 212.232 Air quality program design.

The air quality shall be monitored:

(a) At least once a day and shall include weekly sampling at all sampling ports or points of use in the compressed air distribution system.

(b) At HEPA filter laminar flow equipment.

(c) At the filling lines while filling is in progress and at the same level as the container opening.

(d) In controlled environment areas to assure that the requirements of § 212.221 (a) through (d) are met.

§ 212.233 Water quality program design.

(a) Water quality monitoring shall include:

(1) Sampling and testing of water for manufacturing or final rinsing at least once a day. All sampling ports or points of use in the distribution system shall be sampled at least weekly.

(2) Sampling water for drug product cooling at a point just before entry into the sterilizer at least once each sterilizer cycle and testing by the method described in § 212.226.

(3) Sampling and testing water for cleaning or initial rinsing at least once a week. All sampling ports or points of use in the distribution system shall be sampled at least monthly.

(b) Boiler feed water shall be sampled and tested periodically for the presence of volatile additives.

(c) If three consecutive samples of drug product cooling water exceed microbial limits, the sterilizer loads shall be rejected and shall not be reprocessed.

Subpart M—Sterilization

§ 212.240 Methods of sterilization; minimal processing.

A manufacturing process for terminal sterilization of a large volume parenteral drug product may employ steam, mixtures of air and steam, or superheated water as the sterilizing medium, provided the procedure has been shown to deliver an F_0 of 8 or more.

§ 212.243 Testing of sterilization processes.

(a) The quality control unit shall test the sterilization process to be used in the manufacture or processing of a large volume parenteral drug product in accordance with the requirements of this section. Written records of all testing under this section shall be maintained as specified in § 212.180. Any sterilization process not meeting the requirements of § 212.240 shall not be used. For any sterilization process that it approves, the quality control unit shall establish a maximum microbial count and a maximum microbial heat resistance for filled containers prior to sterilization.

(b) *Heat distribution studies.* Such studies shall be performed on every sterilizer, for each loading configuration, and for every container size. Enough studies shall be performed to confirm that the heat distribution in each autoclave is uniform and reproducible. Each study shall employ a minimum of 10 temperature sensors (calibrated both before and after the study) that are exposed to the sterilizing medium inside of the sterilizer. Heat distribution studies shall be repeated whenever there is any change in the loading pattern or any change in the sterilizer that may affect heat distribution.

(c) *Heat penetration studies.* Such studies shall be performed on each size container within the sterilizing medium to be utilized during production. Such studies shall be performed on large volume parenteral drug products at least as viscous as the most viscous solution to be packaged in the container studied. The studies shall be designed to determine the location of the slowest heating point in the container and to indicate how much time is required to bring the solution at that point to the prescribed processing temperature. Each study shall employ a minimum of 10 containers each with a suitable biological indicator and a temperature sensor submerged in fluid at the previously determined optimal location. In lieu of testing each rigid container size, interpolation may be employed for products in rigid containers if data are available to support interpolation on the types and sizes of containers involved. Heat penetration studies shall be performed on every container size for products in nonrigid containers. Sufficient studies shall be performed to determine whether or not the prescribed F_0 is delivered consistently throughout the sterilizer. The data employed to calculate the F_0 value shall be those data derived beginning when the sterilizer environment has stabilized as shown by reproducible heat distribution studies and the specified sterilizer temperature has been achieved, and ending when cooling is initiated.

§ 212.244 Sterilization process design.

The following factors shall be included in the design of sterilization processes:

(a) *Procedures required to establish uniform heat distribution in the sterilizing medium in the vessel.* Such procedures shall be capable of holding temperatures throughout the sterilizer to within ±0.5° C or ±1° F from the time the product achieves process temperature until the heating portion of the cycle ceases.

(b) *Loading pattern of the sterilizer.* The uniformity of heat distribution shall be independently verified for every loading pattern utilized. The loading pattern must control any contact between containers.

(c) *Initial temperature of the product and sterilizer.* Such temperatures shall not fall below the minimum that has been established for the prescribed sterilization process.

(d) *Venting time.* The time required for venting the sterilizer shall be sufficient to purge it of air and establish a uniform sterilizing medium. This factor is not applicable to water immersion sterilization procedures.

(e) *Product come-up time.* The time required to heat the slowest heating container in the sterilizer to a specified "hold" temperature shall be determined in accordance with § 212.243(c).

(f) *Cooling time.* The initial temperature of the cooling water and the required rate of cooling shall be established.

§ 212.245 Sterilization process controls.

The following procedures and controls shall be applied to the sterilization process employed:

(a) The mercury-in-glass thermometer on each sterilizer shall be tested for accuracy against a known accurate standard thermometer upon installation and at least once every 3 months therefter. Any thermometer found at any time to have a divided mercury column shall be immediately replaced. In the event that there is a variance of 0.5° C or 1° F or more between a recording thermometer and the mercury-in-glass thermometer with which it should agree, both thermometers shall be checked at the conclusion of the cycle. The bleeder for any external thermometer well must emit steam continuously during the entire processing period. The mercury-in-glass thermometer, not the recorder chart, shall be the reference instrument for indicating the chamber temperature unless it is known to have become defective during the sterilization cycle in question. Records shall be maintained reflecting all thermometer calibrations, recalibrations, checking, or replacements in accordance with § 212.183.

(b) Pressure gauges used on sterilizers shall be checked for accuracy at least once every 3 months; such checks shall be recorded in accordance with § 212.183.

(c) Bleeders on sterilizers so equipped shall be wide open during the entire sterilization process. They shall be checked regularly to ensure that they are functioning properly; such checks shall be recorded in accordance with § 212.188 (n).

(d) A minimum of two containers in each sterilizer lot shall be equipped with a suitable means for detecting the F_0 delivered to the solution within. Such data shall be recorded and retained in appropriate batch production records.

(e) The first few containers filled in each batch shall be taken and held under conditions comparable to those under which the remainder of the batch is held until the entire batch is sterilized. These filled containers shall be used to determine the aerobic plate count and the relative heat resistance of the microbial population present. Similarly, the last few containers filled shall be taken and subjected to the same tests. If the microbial count or the microbial heat resistance for the last containers exceeds the maximum level established by the quality control unit in accordance with § 212.243 (a), or if there is a significant increase in the microbial count between the first units collected and the last, the batch shall not be released. The data generated shall be recorded in appropriate batch production and control records in accordance with § 212.188(k).

(f) In the operation of a water-immersion type sterilizer, all containers

shall be submerged during the entire heating, processing, and cooling periods. The head space necessary to control the pressure shall be maintained between the water level and the top of the sterilizer shell. Water circulation shall be maintained continuously during the heating, processing, and cooling periods.

(g) In the operation of a hydrostatic sterilizer, temperatures shall be recorded by an automatic recorder or recorders at the following points:

(1) In the steam chamber between the steam-water interface and the lowest container position.

(2) Near the top and the bottom of each hydrostatic water leg if the process specifies maintenance of particular temperatures in the legs. The data generated shall be recorded in appropriate batch records as indicated in §§ 212.182(d) and 212.188(a).

(h) The speed of the container conveyor chain on hydrostatic sterilizers shall be recorded continuously and such data shall be included in batch production records as indicated in § 212.188(d).

(i) If steam or mixtures of air and steam are used as the sterilizing medium, timing of the sterilization process shall not begin until the sterilizer has been vented and the processing temperature in both the chamber and the drug product solution has been achieved.

(j) If water is used as the sterilizing medium, timing of the sterilization process shall not begin until the processing temperature in the drug product solution has been achieved.

(k) Whenever a batch is subdivided for purposes of sterilization, the lot or control number shall be sufficiently specific to identify the sterilizer in which processing occurred.

Interested persons may, on or before September 29, 1976, submit to the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal. Received comments may be seen in the above office during working hours, Monday through Friday. Ordinarily, 60 days is provided for comment on a proposal, although the Commissioner can reduce or extend this time period for good cause. Because of the nature and extent of the regulations being proposed, the Commissioner has concluded that 120 days should be allowed for public comment. In the absence of extraordinary circumstances, no extension of time for comment will be granted.

Dated: May 21, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Docket No. 76N–0100]

INJECTABLE DRUG PRODUCTS

Request for Comments and Information Regarding Small Volume Parenteral Drug Products

The Food and Drug Administration is requesting comments and information regarding the applicability of proposed large volume parenteral regulations to small volume parenteral drug products; comments by August 30, 1976.

Elsewhere in this issue of the FEDERAL REGISTER the Commissioner of Food and Drugs is proposing to amend Chapter I of Title 21 of the Code of Federal Regulations by adding new Part 212. The proposal sets forth requirements for current good manufacturing practice (CGMP) in the manufacture, processing, packing, or holding of large volume parenteral (LVP) drug products for human use.

Although these proposed regulations are directed at terminally sterilized single-dose containers of 100 milliliters or more, the Commissioner considers that many of the proposed requirements for LVP drug products will eventually be applied to all terminally sterilized single-dose injectable drug products, regardless of the volume of the container. This will necessitate issuing a proposal at a future date for similar regulations for small volume injectable drug products. The Commissioner therefore invites comments at this time from all interested persons, and particularly from manufacturers of injectable drug products, regarding the applicability of the proposed Part 212 to terminally sterilized single-dose injectable drug products for human use that are less than 100 milliliters in volume.

In addition, the Commissioner invites comments and information regarding current manufacturing practices for any terminally sterilized small volume parenteral drug product, regardless of the sterilization process used.

The Commissioner requests that information submitted include brief descriptions with flow diagrams of the processes involved and descriptions of the types of drug product containers used.

Any comments or other information should be forwarded on or before August 30, 1976 to the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852.

Dated: May 21, 1976.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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